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CARDIOVASCULAR MEDICINE

Progressive coronary calcification despite intensive lipid-lowering treatment: a randomised controlled trial

E S Houslay, S J Cowell, R J Prescott, J Reid, J Burton, D B Northridge, N A Boon, D E Newby, on behalf of the Scottish Aortic Stenosis and Lipid Lowering Therapy, Impact on Regression (SALTIRE) trial Investigators



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See end of article for authors' affiliations

Correspondence to:
Professor David E Newby,
SU.314 Chancellor's
Building, University of
Edinburgh, Edinburgh
EH16 4SA, UK; d.e.
newby@ed.ac.uk

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Objectives: To evaluate the effect of intensive lipid-lowering treatment on coronary artery calcification in a substudy of a trial recruiting patients with calcific aortic stenosis.

Methods: In a double blind randomised controlled trial, 102 patients with calcific aortic stenosis and coronary artery calcification were randomly assigned by the minimisation technique to atorvastatin 80 mg daily or matched placebo. Coronary artery calcification was assessed annually by helical computed tomography.

Results: 48 patients were randomly assigned to atorvastatin and 54 to placebo with a median follow up of 24 months (interquartile range 24–30). Baseline characteristics and coronary artery calcium scores were similar in both groups. Atorvastatin reduced serum low density lipoprotein cholesterol (–53%, $p < 0.001$) and C reactive protein (–49%, $p < 0.001$) concentrations whereas there was no change with placebo (–7% and 17%, $p > 0.95$ for both). The rate of change in coronary artery calcification was 26%/year (0.234 (SE 0.037) log arbitrary units (AU)/year; $n = 39$) in the atorvastatin group and 18%/year (0.167 (SE 0.034) log AU/year; $n = 49$) in the placebo group, with a geometric mean difference of 7%/year (95% confidence interval –3% to 18%, $p = 0.18$). Serum low density lipoprotein concentrations were not correlated with the rate of progression of coronary calcification ($r = 0.05$, $p = 0.62$).

Conclusion: In contrast to previous observational studies, this randomised controlled trial has shown that, despite reducing systemic inflammation and halving serum low density lipoprotein cholesterol concentrations, statin treatment does not have a major effect on the rate of progression of coronary artery calcification.

Coronary artery calcification is an independent risk factor for coronary heart disease, with even low coronary calcium scores doubling the risk of coronary events.¹ The relative risk associated with coronary calcification is greater than that associated with established factors such as smoking, hypertension and diabetes mellitus. Progression of coronary artery calcification is associated with a higher incidence of coronary events even among people who are asymptomatic at the time of initial scanning.² Thus, not only is the presence of coronary artery calcification indicative of atheromatous plaque disease but its progression may correspond with cardiovascular event rates.

Statin treatment has a proven role in the primary^{3–4} and secondary prevention^{5–8} of cardiovascular disease, with incremental benefits seen with more intensive reductions in serum cholesterol concentrations.⁸ Previous studies^{9–10} have reported that statins can halt the progression and may even induce regression of coronary artery calcification. Indeed, the rate of progression of coronary artery calcification correlates with the average serum low density lipoprotein (LDL) cholesterol concentration.⁹ This has led to the use of computed tomography to monitor disease progression and response to treatment, particularly with statins. Two recent trials, however, did not show a benefit of statin on the progression of coronary artery calcification in asymptomatic people.^{11–12}

The SALTIRE (Scottish Aortic Stenosis Lipid lowering Therapy, Impact on Regression) trial was a prospective double blind, randomised controlled study of intensive lipid-lowering treatment of patients with calcific aortic stenosis.¹³ As part of this trial, aortic valve and coronary

artery calcium scores are measured by helical computed tomography. The objective of this substudy was to assess the effect of atorvastatin 80 mg daily on the rate of progression of coronary artery calcification in patients with calcific aortic stenosis.

METHODS

Patient population

Patients aged > 18 years with calcific aortic stenosis (grade 1–3 calcification on echocardiography¹⁴) and a peak post-valve velocity of ≥ 2.5 m/s were recruited from eight hospital centres across the southeast of Scotland. Exclusion criteria were women of childbearing potential without contraception, active or chronic liver disease, history of alcohol or drug misuse, severe mitral stenosis (valve area < 1 cm²), severe mitral or aortic regurgitation,¹⁵ major left ventricular dysfunction (ejection fraction $< 35\%$), planned aortic valve replacement, intolerance to statins, patients who were taking or would in the opinion of the treating physician benefit from statins, baseline serum total cholesterol of < 4.0 mmol/l, and permanent pacemaker or cardiodefibrillator. For the substudy, we also excluded patients who had no coronary artery calcification on computed tomography. The study was conducted with the approval of all the regional research ethics committees and in accordance with the Declaration of

Abbreviations: AU, arbitrary units; BELLES, Beyond Endorsed Lipid Lowering with EBT Scanning; CRP, C reactive protein; LDL, low density lipoprotein; SALTIRE, Scottish Aortic Stenosis Lipid Lowering Therapy, Impact on Regression

Helsinki. Written informed consent was obtained from each participant.

Study protocol

Between March 2001 and April 2002, the blinded study coordinator randomly assigned eligible patients by the minimisation technique¹⁶ with a dedicated locked computer program (Edinburgh University), which incorporated eight baseline variables: age, sex, smoking habit, hypertension, diabetes mellitus, serum cholesterol concentration, peak aortic jet velocity and aortic calcium score. Patients were assigned either to atorvastatin 80 mg daily or matched placebo (Pfizer, Tadworth, UK) as a single daily dose in numbered containers.

Patients were assessed at baseline, two months, six months and every six months thereafter for a minimum of two years. Clinical evaluation included assessment of functional status, adverse events and biochemical blood analysis. Serum high sensitivity C reactive protein (CRP) concentrations were determined by a highly sensitive immunonephelometric method (Dade Behring, Milton Keynes, UK) as previously described.¹⁷ All patients underwent computed tomography within the month before randomisation to study treatment and at each annual visit. Randomly assigned patients who were later treated with an open label statin by their attending physician were immediately scanned and withdrawn from further observation.

Computed tomography

A single blinded operator performed computed tomography with a double helix scanner (Twin II Flash; Philips Medical Systems (UK), Stevenage, UK) calibrated against a standard phantom. Images were acquired in 2.7 mm slices (with a 0.75 s full 360° scan mode) through the region of the coronary arteries with a pitch of 0.7 and an increment of 1.3 mm during held inspiration. Exposure factors were 120 kV at 270 mA and the scan angle was 360°. Images were analysed off line with an automated, computerised software program (Picker cardiac scoring). This uses an Agatston scoring method,¹⁸ producing sensitivity and specificity comparable with electron beam computed tomography.¹⁷ Scans were scored by both the Agatston (130 HU threshold) and the modified Agatston (90 HU threshold) methods.¹⁹ The Agatston method has been shown to reduce interobserver and interscan variation compared with the threshold of 90 HU.²⁰ To assess the reproducibility of the method, repeated baseline computed tomography scans were recorded within four weeks of each other in an unselected random sample of 16 patients.

Data analysis and statistics

Coronary artery calcium scores are expressed in arbitrary units (AU) based on the 130 HU threshold. The calcium scores and high sensitivity CRP concentrations were not normally distributed and data are presented as median

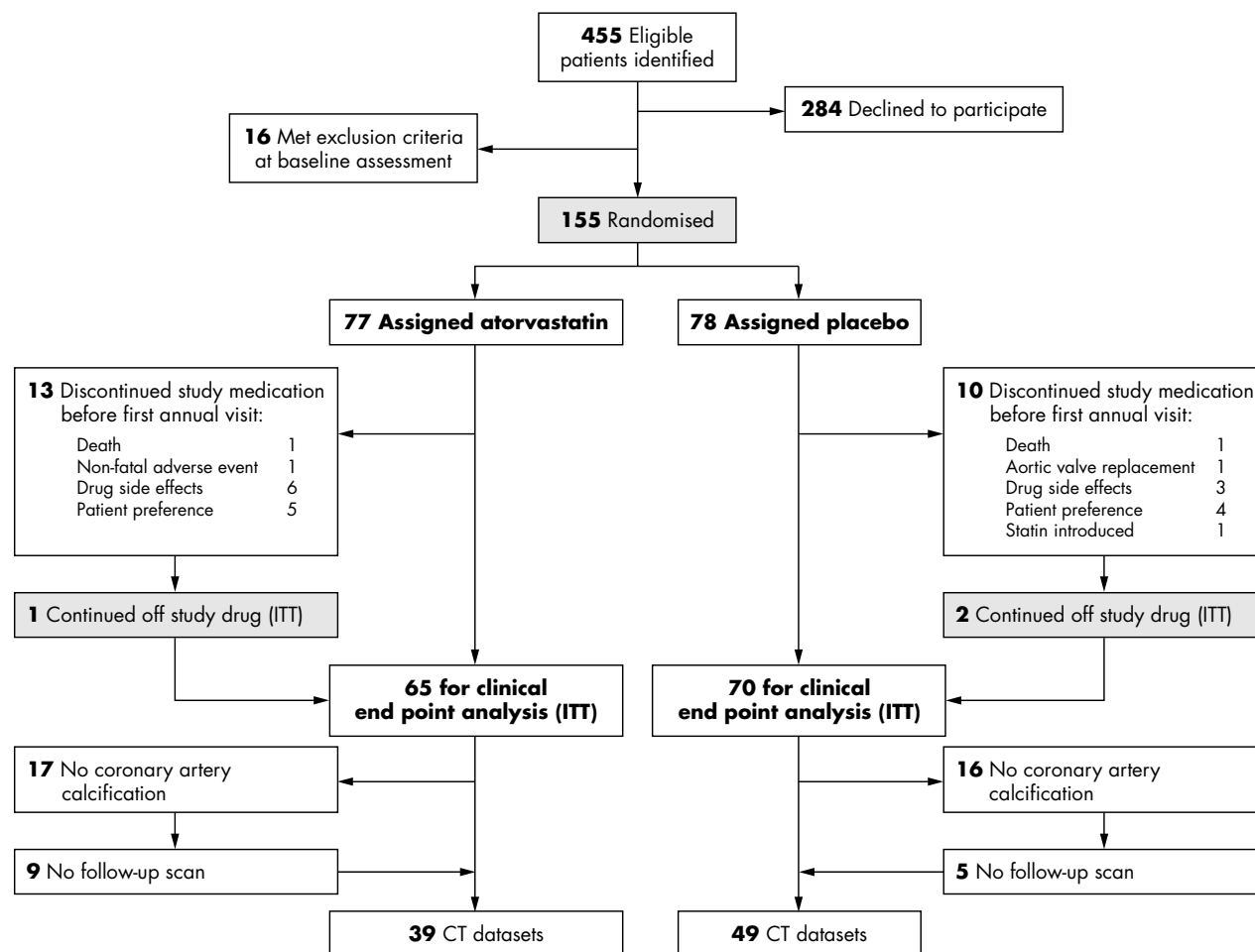


Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram of patients recruited into the trial and substudy. CT, computed tomography; ITT, intention to treat.

Table 1 Baseline characteristics of participants with calcific aortic stenosis in the treatment groups

Characteristic	Atorvastatin (n = 39)	Placebo (n = 49)
Age (years)	70 (8)	70 (9)
Men	74%	78%
Body mass index (kg/m ²)	29 (5)	28 (5)
Cardiovascular risk factors		
Hypertension	22	28
Hyperlipidaemia	3	2
Diabetes mellitus	0	2
Current smoker	5	10
Cardiovascular disease		
Coronary heart disease	7	13
Cerebrovascular disease	5	7
Peripheral vascular disease	3	7
Drug history		
Aspirin	17	26
ACE inhibitor	7	8
β blocker	11	15
Warfarin	4	8
Blood pressure (mm Hg)		
Systolic	143 (18)	140 (19)
Diastolic	82 (11)	78 (11)
Lipid profile		
Total cholesterol (mmol/l)	5.7 (0.9)	5.5 (0.9)
LDL cholesterol (mmol/l)	3.6 (0.8)	3.4 (0.7)
HDL cholesterol (mmol/l)	1.5 (0.4)	1.5 (0.4)
Total cholesterol:HDL	4.2 (1.2)	4.0 (1.0)
Triglycerides (mmol/l)	1.5 (0.8)	1.4 (0.7)
Coronary calcification score (AU)		
Left anterior descending artery	112 (40–285)	207 (76–461)
Circumflex artery	0 (0–9)	0 (0–4)
Right coronary artery	0 (0–29)	0 (0–0)
Total coronary score	195 (57–448)	235 (83–526)
Log total coronary score (log AU)	2.16 (0.68)	2.30 (0.65)

Continuous variables stated as mean (SD) or median (interquartile range).

ACE, angiotensin-converting enzyme; AU, arbitrary unit; HDL, high density lipoprotein; LDL, low density lipoprotein.

(interquartile range) or mean (SD) after logarithmic transformation (log AU). The primary end point, the rate of change of coronary calcium scores, was analysed with random coefficient models^{13–21} after logarithmic transformation of the scores. In summarising the data, we calculated the change in coronary artery calcium scores by dividing the change between the baseline and final scores by the duration of follow up. Rate of change in coronary calcium score is expressed as percentage change per year or as absolute change in the logarithm of the coronary artery calcium score. Reproducibility was assessed by the method of Bland and Altman.²¹ As well as tests of significance, 95% confidence intervals are reported as appropriate. Significance was taken as a two-sided $p < 0.05$.

RESULTS

Of 155 patients recruited into the SALTIRE trial, 102 had coronary calcification at baseline (fig 1), of whom 88 had at least two scans. Coronary calcification predominated in the left anterior descending artery (100% of patients) although it was also present in the circumflex (33%) and right (27%) coronary arteries. Baseline characteristics and coronary artery calcium scores were well matched in both treatment groups (table 1) in the 88 evaluable participants.

Reproducibility

The reproducibility of the left anterior descending coronary score and of the total coronary score was examined with the approach of Bland and Altman.²¹ Without transformation, the difference between replicate observations tended to increase with the magnitude of the measurement. After logarithmic transformation, higher values showed stable

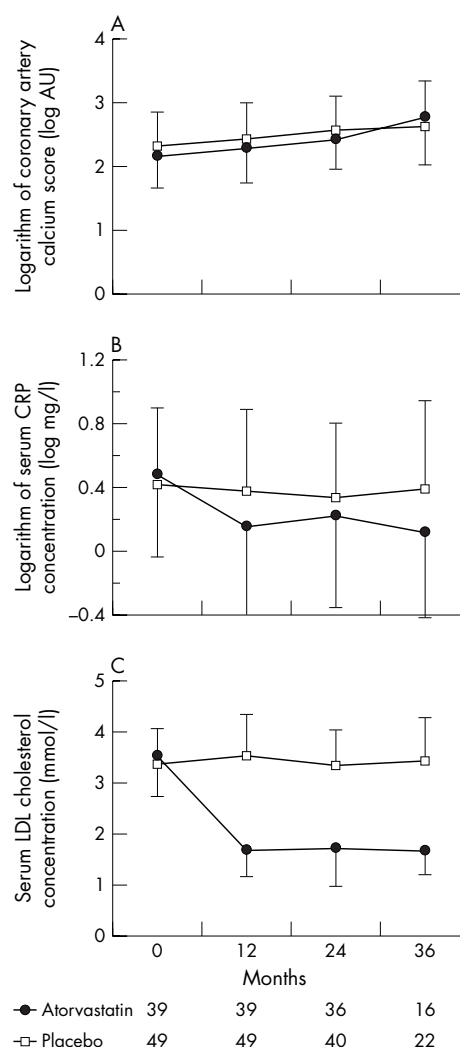


Figure 2 Progression of (A) coronary artery calcification, (B) serum C reactive protein (CRP) concentrations ($p < 0.001$, atorvastatin v placebo) and (C) serum low density lipoprotein (LDL) cholesterol concentrations ($p < 0.001$, atorvastatin v placebo) in patients treated with atorvastatin 80 mg daily or matched placebo. AU, arbitrary units.

differences, but differences were higher at the lowest scores. Overall, the differences on the log scale correspond to a coefficient of variation of 28% for both variables, but when the analysis was restricted to the 10 pairs with a geometric mean score above 100, the coefficient of variation was 10% for both variables.

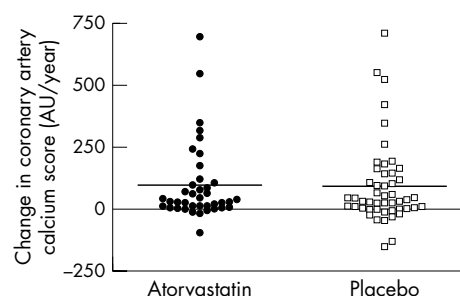


Figure 3 Absolute rate of change in coronary calcium score expressed in arbitrary units (AU) per year for patients treated with atorvastatin 80 mg or matched placebo.

Effect of atorvastatin treatment

Patients were followed up for a median of 24 months (interquartile range 24–30). Atorvastatin 80 mg daily more than halved serum LDL cholesterol concentrations (53 (SD 19)%, $p < 0.001$), whereas placebo had no effect (fig 2). This reduction in serum LDL cholesterol concentrations was associated with a major decrease in serum CRP concentrations from 1.95 (interquartile range 1.15–4.86) to 1.00 mg/l (0.49–2.31) (Wilcoxon signed rank test $p < 0.001$) (fig 2). Atorvastatin was well tolerated: two patients in the placebo group and five patients in the atorvastatin group discontinued the treatment, predominantly as a result of gastrointestinal upset. One patient taking atorvastatin had an increase in creatine kinase of > 5 times the upper limit of normal without symptoms of myositis and was withdrawn at the request of the Data Monitoring Committee. There were no cases of rhabdomyolysis.

Coronary artery calcium score

Atorvastatin did not affect the rate of progression of the coronary artery calcium score (fig 2). Similar results were obtained when the 90 HU threshold was used (42 (SD 73)%/year in the atorvastatin group and 29 (SD 37)%/year in the placebo group, $p = 0.24$). Serum LDL cholesterol concentrations did not correlate with the rate of progression of coronary artery calcification ($r = 0.05$, $p = 0.62$).

The rates of change of coronary artery calcium scores were primarily analysed on the logarithms of the scores by random coefficients models.²² This showed no difference between the average rates of change in the two treatment arms ($p = 0.18$). The mean coronary calcium score increased by 0.234 (SE 0.037) log AU/year in the atorvastatin group and 0.167 (SE 0.034) log AU/year in the placebo group. These figures correspond to a 26%/year increase in the atorvastatin group and 18%/year in the placebo group. The geometric mean (adjusted for baseline) is 7% higher at one year with atorvastatin than with placebo, with 95% confidence limits ranging from 3% lower to 18% higher. Figure 3 summarises the observed annual changes in coronary calcium scores, calculated from the first to the last visit.

As anticipated in such a modest clinical trial, all cause mortality, cardiovascular mortality or cardiovascular hospitalisation did not differ significantly between the two groups.

DISCUSSION

We have confirmed that, despite major reductions in serum LDL cholesterol and CRP concentrations, atorvastatin 80 mg daily did not halt the progression, or induce regression, of coronary artery calcification in patients with calcific aortic stenosis. Consistent with recent trials of asymptomatic people,^{11, 12} our findings contrast notably with previous observational studies and suggest that the potential beneficial effects on coronary artery calcification have been overestimated.

Previous observational and non-randomised prospective studies^{9, 10} have suggested that reductions in serum LDL cholesterol concentrations decrease the progression of coronary calcification. Not all observational studies, however, have had consistent findings. In the largest observational study of 182 patients, Hecht and colleagues²³ recently found no difference in the progression of coronary calcium scores in patients who were maintained on lipid-lowering treatment and achieved significant reductions in serum LDL cholesterol concentrations. Observational data may be misleading and prospective randomised controlled trials are necessary to confirm or to refute these interesting preliminary observations. The recent BELLES (Beyond Endorsed Lipid Lowering with EBT Scanning) trial¹² found no differential effect between pravastatin (40 mg daily) and atorvastatin (80 mg

daily) on the progression of coronary artery calcification in 615 hyperlipidaemic postmenopausal women. Study follow up was brief (one year), however, and there was no placebo control group. The St Francis Heart Study¹¹ randomly assigned 1005 asymptomatic middle-aged men and women with high coronary artery calcium scores to combination atorvastatin 20 mg, vitamin C 1 g, and vitamin E (α tocopherol) 1000 U daily or to matching placebos. After 4.3 years of follow up, the rate of progression of coronary artery calcification did not differ.

We have conducted a double blind randomised controlled trial with helical computed tomography in patients with aortic stenosis. Minimisation technique ensured good matching of the baseline characteristics of the patient population and reproducibility studies confirmed the validity of our repeated assessments. Although documenting very similar rates of progression of coronary calcification to previous studies,^{9, 10, 23} we have not observed a reduction in coronary calcification with intensive lipid-lowering treatment despite more than halving serum LDL cholesterol concentrations.

Statins have been extremely successful in the primary and secondary prevention of cardiovascular disease. Why then have we and others not observed a beneficial effect of statin on coronary artery calcification? Unstable atherosclerotic plaques have a large lipid-rich core, a preponderance of macrophages and foam cells, and a thin fibrous cap containing few smooth muscle cells.²⁴ It has been suggested that calcified lesions may be relatively more stable,²⁵ indicating a possible protective role of calcification in coronary plaques. Statins produce many of their beneficial effects through plaque stabilisation. In both primate²⁶ and swine²⁷ models, antiatherosclerotic interventions are associated with an increase in vascular fibrous tissue and calcification. This calcium deposition continues during the initial phase of plaque regression due to the death of foam cells and an increase in necrotic tissue. Thus, vascular calcification may have a role in the initial stabilisation of atherosclerotic plaques. This is consistent with our findings and would account for the lack of effect on the progression of coronary artery calcification despite a reduction in serum CRP concentrations.

After the initial stabilisation of the atherosclerotic plaque, subsequent progression of coronary calcification would be anticipated to be inhibited. The present study was brief, and follow up was only continued for a median of two years. It would be important to extend our observations to five or more years to assess properly the impact of statin on the long-term progression of coronary artery calcification. It should be acknowledged, however, that the clinical benefits of statin are apparent within the first few years,^{6–8} and in some cases the first few months,²⁸ of treatment. Moreover, the St Francis Heart Study showed no beneficial effects despite 4.3 years of follow up.⁹

On the basis of previous non-randomised studies,¹⁰ the practice of performing serial computed tomography to monitor disease progression and the response to treatment has become widespread, especially in North America. Our data, and those of the St Francis Heart Study¹¹ and the BELLES study,¹² indicate that repeated scanning to assess response to statin is not justified. Indeed, the radiation dose incurred for such serial scans poses potential health risks, particularly when multidetector computed tomography scanners are used.

Study limitations

Several factors should be taken into account when considering the results of our study. This was a substudy of the SALTIRE trial¹³ that recruited only patients with calcific aortic stenosis. Our findings are consistent, however, with two

recent randomised controlled trials in asymptomatic younger people without valvular heart disease.^{11 12} Our study therefore suggests that failure of statins to restrict the progression of coronary artery calcification can be extended to include patients with valvular heart disease as well as older populations. Moreover, our findings suggest that the lack of benefit seen in the St Francis Heart Study is not attributable to the modifying effects of antioxidant vitamins.

When compared with electron beam computed tomography, the accuracy of helical computed tomography in detecting coronary artery calcification has been questioned.^{18 29} Technological advances have also meant that double helical scanners have now been overtaken by 64-slice scanners. At trial inception, the double helix scanner was the latest technology, and it would have been inappropriate to replace the scanner during the conduct of the trial. Moreover, our approach has been previously validated²¹ and we have shown good reproducibility of coronary artery calcification scores in patients with scores of > 100 AU. We do not believe the absence of a major beneficial effect on coronary artery calcification is attributable to our methods. We acknowledge that our population size is modest; however, the 95% confidence intervals can exclude a relative reduction in progression of coronary artery calcification of > 3%/year. We therefore suggest that if lipid-lowering treatment does reduce the progression of coronary artery calcification then the effect is rather small.

The method of quantification of coronary artery calcification is controversial. The Agatston method is traditionally used but this may overestimate the coronary calcium score in newer generation scanners with reduced slice thickness due to partial voluming. More recent methods include the volume³⁰ and the coronary calcium mass³¹ scores, although neither is superior to the Agatston score in terms of reproducibility from consecutive scans in an individual patient.³²

Conclusion

We conclude that intensive lipid-lowering treatment does not halt the progression, or induce regression, of coronary artery calcification. Although coronary artery calcium scores correlate well with the presence of atherosclerosis and predict future coronary risk, our findings confirm that monitoring progression of coronary artery calcification to assess the response to lipid-lowering treatment has no role.

Authors' affiliations

E S Houslay, S J Cowell, N A Boon, D E Newby, Department of Cardiology, Royal Infirmary, Edinburgh, UK

R J Prescott, Public Health Sciences, University of Edinburgh, Medical School, Edinburgh, UK

J Reid, J Burton, Department of Radiology, Borders General Hospital, Melrose, Roxburghshire, UK

D B Northridge, Department of Cardiology, Western General Hospital, Edinburgh, UK

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Competing interests: DEN and NAB hold unrestricted educational grant awards from Pfizer (UK) Ltd. DEN, DBN and NAB have undertaken paid consultancy and served on advisory boards for Pfizer (UK) Ltd.

Author contributions: ESH, SJC, JB and JR acquired the data. ESH and RP analysed the data. DEN, DBN and NAB conceived and designed the study. All authors contributed to the writing, revision and approval of the paper.

SALTIRE research team: Lorraine Anderson, Corrine Bell, Margaret Bland, Peter Bloomfield, Sharon Cameron, Nicholas Cruden, Jean Cunningham, Hayley Cuthbertson, Laura Flint, Margaret Henderson,

Dawn Lyle, Maureen O'Donnell, Finney Paterson, Karen Paterson, Robin Prescott, Simon Robinson, Heather Spence, Julie Ticknal and Audrey White

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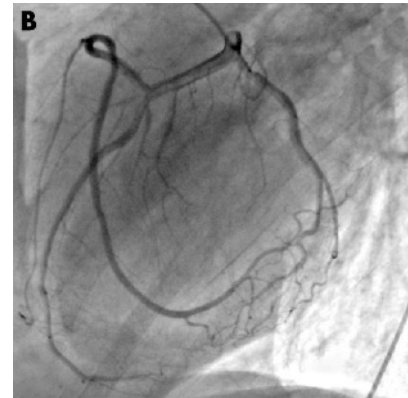
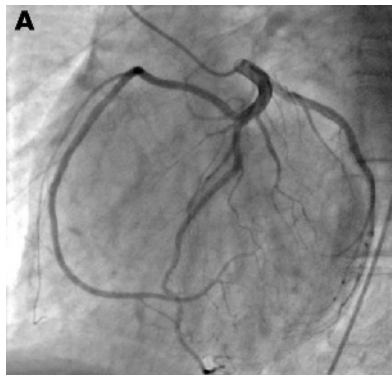
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Anomalous origin of right coronary artery from the mid left anterior descending coronary artery

A 59-year-old woman underwent diagnostic coronary angiography with a history of atypical chest pain and an inconclusive treadmill exercise tolerance test. Cine-angiogram revealed an unusual origin of the right coronary artery (RCA) arising from the mid left anterior descending coronary (LAD) artery and coursing to the right, anterior to the right ventricular outflow tract. Such an anomaly is unusual and has not been listed in the classification of such anomalies.

Coronary anomalies are seen in about 1% of cineangiograms. While some anomalies have been associated with adverse clinical outcomes, most are benign. The RCA has been documented to have an anomalous origin from the left anterior coronary sinus and



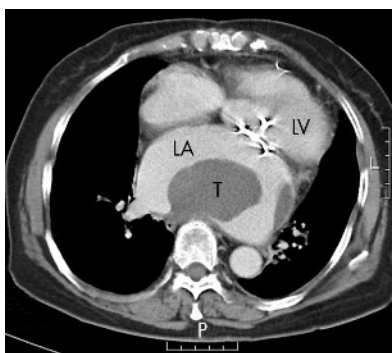
pulmonary trunk, but the origin of the RCA from the LAD has not been reported before.

P Saravanan, P Mennim, J E Hancock
saravananpl@aol.com

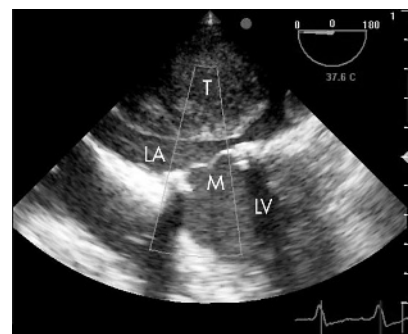
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Huge left atrial thrombus in a patient with mitral bioprosthesis

A 77-year-old woman had suffered from atrial fibrillation and rheumatic mitral stenosis for more than 20 years. She underwent mitral valve replacement with bioprosthesis six months before her admission. Inadequate anticoagulation treatment was noted during the follow-up period. She presented with unsteady gait and dizziness to our emergency room. Brain magnetic resonance images confirmed cerebellar infarction. Echocardiography was arranged to search for the possible embolus source, and revealed a huge left atrial thrombus. Because of the thrombus burden and recent stroke, redo cardiac surgery was proposed three weeks after the cerebrovascular event. The preoperative computed tomography (CT) for redo surgery found a large left atrial mass (left panel). During the less invasive cardiac surgery via right small thoracotomy, transoesophageal echocardiography



Computed tomography demonstrating a huge mass in an enlarged left atrium. LA, left atrium; LV, left ventricle; T, thrombus.



Transoesophageal echocardiography revealing a heavy thrombus burden in the posterior wall of left atrium with the bioprosthesis in the mitral position (M).

revealed the significant thrombus burden again (right panel). The bioprosthesis was found to be functioning well and thrombus-free. Additional left atrial appendage closure and endocardial

ablation were performed to reduce the risk of future thromboembolism.

K-M Chiu, T-Y Lin, S-H Chu
kmchiu@yahoo.com.tw